CLAIMS

What is claimed is:

1. A modified HCV NS3 protease comprising at least one substitution in HCV NS3 protease of a hydrophobic α-helix 0 amino acid residue to a hydrophilic amino acid residue.

2. A modified HCV NS3 protease of claim 1 wherein the hydrophobic α-helix 0 amino acid residues are selected from the group consisting of Leu_{13}, Leu_{14}, Ile_{17}, Ile_{18}, and Leu_{21}.

3. The modified HCV NS3 protease of claim 1 wherein said HCV NS3 protease comprises approximately residues 1-181 of the amino acid sequence of HCV NS3 as shown in SEQ ID NO: 1.

4. The modified HCV NS3 protease of claim 1 further comprising at least one substitution of a hydrophobic amino acid residue not in the α-helix 0 to a hydrophilic amino acid residue.

5. The modified HCV NS3 protease of claim 1 further comprising at least one substitution of a non-zinc-binding cysteine residue to a non-cysteine amino acid residue.

6. The modified HCV NS3 protease of claim 2 comprising at least one substitution selected from the group consisting of: Leu_{13} is substituted to Glu , Leu_{14} is substituted to Glu, Ile_{17} is substituted to Gln, Ile_{18} is substituted to Glu, and Leu_{21} is substituted to Gln.

7. The modified HCV NS3 protease of claim 2 comprising at least one substitution selected from the group consisting of Leu_{13} is substituted to Glu , Leu_{14} is substituted to Gln, Ile_{17} is substituted to Gln, Ile_{18} is substituted to Lys, and Leu_{21} is substituted to His.

8. The modified HCV NS3 protease of claim 2 comprising at least one substitution selected from the group consisting of Leu_{13} is substituted to Glu , Leu_{14} is substituted to Glu, Ile_{17} is substituted to Gln, Ile_{18} is substituted to Gln, and Leu_{21} is substituted to Glu.

9. The modified HCV NS3 protease of claim 2 comprising at least one substitution selected from the group consisting of Leu_{13} is substituted to Asn, Leu_{14} is substituted to Gln, Ile_{17} is substituted to Glu, Ile_{18} is substituted to Lys, and Leu_{21} is substituted to Glu.

10. The modified HCV NS3 protease of claim 2 comprising at least one substitution selected from the group consisting of Leu_{13} is substituted to Glu , Leu_{14} is substituted to Gln, Ile_{17} is substituted to Asp, Ile_{18} is substituted to Glu, and Leu_{21} is substituted to Glu.

11. The modified HCV NS3 protease of claim 2 comprising at least one substitution selected from the group consisting of Leu_{13} is substituted to Glu, Leu_{14} is substituted to Glu, Ile_{17} is substituted to Glu, Ile_{18} is substituted to Gln, and Leu_{21} is substituted to Glu.

12. The modified HCV NS3 protease of claim 2 wherein Leu_{13}, Leu_{14}, Ile_{17}, Ile_{18}, and Leu_{21} are substituted to hydrophilic amino acid residues.

13. A modified HCV NS4a-NS3 fusion protease comprising a modified HCV NS3 protease of claim 1 fused to a HCV NS4a or a modified HCV NS4a.

14. The modified HCV NS4a-NS3 fusion protease of claim 13 wherein said HCV NS4a comprises approximately residues 21-31 of full-length HCV NS4a as shown in SEQ ID NO: 26.

15. The modified HCV NS4a-NS3 fusion protease of claim 13 wherein the HCV NS4a that is altered to form said modified HCV NS4a comprises approximately residues 21-31 of full-length HCV NS4a as shown in SEQ ID NO: 26.

16. The modified HCV NS4a-NS3 fusion protease of claim 13 further comprising a linker.

17. The modified HCV NS4a-NS3 fusion protease of claim 16 wherein the linker comprises an optimized linker sequence.

18. The modified HCV NS4a-NS3 fusion protease of claim 13 wherein the HCV NS4a or modified HCV NS4a is linked to the amino terminus of the modified HCV NS3 protease.

19. The modified HCV NS4a-NS3 fusion protease of claim 17 wherein the optimized linker sequence is Ser-Gly-Asp-Thr where Ser corresponds to HCV NS4a residue Ser_{32} and Thr corresponds to HCV NS3 residue Thr_4.

20. The modified HCV NS4a-NS3 fusion protease of claim 13 wherein the modified HCV NS4a comprises at least one substitution of a hydrophobic amino acid residue to a hydrophilic amino acid residue.

21. The modified HCV NS4a-NS3 fusion protease of claim 20 wherein NS4a residue 30 is substituted to a hydrophilic amino acid residue.

22. The modified HCV NS4a-NS3 fusion protease of claim 21 wherein the hydrophilic amino acid residue is Asn.

23. A modified HCV NS4a-NS3 fusion protease of claim 13 comprising an amino acid sequence selected from the group consisting of: SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, and SEQ ID NO: 22.

24. A nucleic acid molecule comprising a nucleotide sequence coding for a modified HCV NS3 protease of claim 1.

25. A nucleic acid molecule comprising a nucleotide sequence coding for a modified HCV NS4a-NS3 protease of claim 13.

26. A nucleic acid molecule of claim 25 wherein the nucleotide sequence is selected from the group consisting of: SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, and SEQ ID NO: 23.

27. A nucleic acid molecule of claim 25, wherein said nucleic acid molecule comprises all or a portion of the plasmid contained in a cell of ATCC culture accession number 207040.

28. A nucleic acid molecule of claim 25, wherein said nucleic acid molecule comprises all or a portion of the plasmid contained in a cell of ATCC culture accession number 207041.

29. A nucleic acid molecule comprising a nucleotide sequence which is complementary to the nucleotide sequence of claim 24, 25 or 26.

30. A vector comprising the nucleic acid molecule of claim 24, 25, 26 or 29.

31. A host cell comprising the vector of claim 30.

32. A cell as defined by ATCC culture accession number 207040.

33. A cell as defined by ATCC culture accession number 207041.

34. A method for producing a modified NS3 protease comprising:

a) culturing the host cell of claim 1 under suitable conditions so as to produce the modified NS3 protease; and

b) recovering the modified NS3 protease so produced.

35. A method for producing a modified NS4a-NS3 protease comprising:

a) culturing the host cell of claim 13 under suitable conditions so as to produce the modified NS4a-NS3 protease; and

b) recovering the modified NS4a-NS3 protease so produced.

36. A modified HCV NS3 protease or modified HCV NS4a-NS3 fusion protease having solubility of greater than 30 mg/ml in the absence of detergents.

37. A modified HCV NS3 protease or modified HCV NS4a-NS3 fusion protease usable for NMR spectroscopy.